TABLE C-4. (continued)

Constituent	Setting	Average concentration	Reference
	Office	5.0 ppm	Harke, 1974
	Car	40.0 ppm (peak)	Harke and Peters, 1974
	Train	20.0 ppm	Harmsen & Effenberger, 1957
	Public places	8.0 ppm	Perry, 1973
	Rooms	15.0 ppm	Portheine, 1971
	Varied	10.0 ppm	Stebben et al., 1977
	Conference rooms	8.0 ppm (peak)	Slavin and Hertz, 1975
	Offices	3.0 ppm	Szadkowski et al., 1976
Nicotine	Varied	100.0 $\mu g/m^3$	Badré et al., 1978
	Submarines	30.0 $\mu g/m^3$	Cano et al., 1970
	Train	2.0 $\mu g/m^3$	Harmsen & Effenberger, 1957
	Varied	6.0 $\mu g/m^3$	Hinds & First, 1975
	Restaurants	15.0 $\mu g/m^3$	Muramastu et al., 1984
N-nitrosodi-methylamine	Varied	100.0 ng/m^3	Brunnemann & Hoffmann, 1978, and Brunnemann et al., 1978
	Restaurants	25.0 ng/m^3	Stehlik et al., 1982

(continued on following page)

TABLE C-4. (continued)

Constituent	Setting	Average concentration	Reference
RSP	Varied	200.0 $\mu g/m^3$	Repace and Lowrey, 1980
	Varied	300.0 $\mu g/m^3$	Repace and Lowrey, 1982
	Coffeehouses	1000.0 $\mu g/m^3$	Just et all, 1972
	Hospital	30.0 $\mu g/m^3$	Neal et al., 1978
	Residences	60.0 $\mu g/m^3$	Spengler et al., 1981
	Offices	130.0 $\mu g/m^3$	Weber and Fischer, 1980
	Offices	50.0 $\mu g/m^3$	Nelson et al., 1982
	Restaurants	1000.0 $\mu g/m^3$	Husgafvel-Pursiainen et al., 1986
	Houses	150.0 $\mu g/m^3$	Brunekreef and Beleij, 1982
	Tavern	600.0 $\mu g/m^3$	Cuddleback et al., 1976
	Residences	30.0 $\mu g/m^3$	Dockery and Spengler, 1981
	Arenas	400.0 $\mu g/m^3$	Elliott and Rowe, 1975
Acetone	Varied	1.0 mg/m^3	Badré et al., 1978
Sulfates	Residences	5.0 $\mu g/m^3$	Dockery and Spengler, 1981

*Adapted from Repace (1987).

Application of the dosimetry model of ETS beyond the initial step of predicting inhalation becomes hampered by the large amount of detailed biological information required for the carcinogens in tobacco smoke. This limitation is more applicable to the vapor phase, however, than to the particulate phase. In the latter case, many of the dosimetric characteristics are largely dependent on the distribution of the size and density of particulates rather than chemical-specific properties. To continue illustration of our example as possible, and also to identify where information is available and where it is needed, we will consider the particulate phase further but not the vapor phase. The information available for calculation by lung regions is disparate, so assumptions will be made explicit as required to complete calculations for lung dose from the particulate phase for our example. We have stopped short of introducing assumptions that do not seem "reasonable," however, simply for the sake of illustration. The calculated values may be viewed as approximations, vis-a-vis the assumptions used. In any event, intake of vapor phase components is included in Table C-3.

Fortunately, one of the major constituents of interest in tobacco smoke, nicotine, has been sufficiently studied that much of the information required for prediction of lung and systemic organ dose of nicotine and the metabolite cotinine can be calculated for our example, including both the vapor and particulate phases for active and passive smoking. Nicotine dosimetry is particularly relevant because it is the addictive factor in active smoking and is a pre-cursor of tobacco specific nitrosamines, at least one of which (NNK) is a potent carcinogen (Hoffmann and Hect, 1989). Also, nicotine forms the tobacco-specific metabolite cotinine, widely considered to be the preferred biomarker for ETS exposure. Calculations for nicotine/cotinine are in Section C.6.

C.4. UPTAKE OF PARTICULATE PHASE CHEMICALS

Due to lack of data on uptake of vapor phase components by lung tissue, only the uptake of particulate phase chemicals can be considered here. For chemicals in the vapor phase, the proportionality constant to convert from intake to uptake may differ between chemicals. The lack of chemical-specific data on uptake from the vapor phase is a major limitation for comparison of carcinogenicity of tobacco smoke to active and passive smokers. There is a pressing need for research on concentration ratios (air:tissue) for vapor phase components of ETS.

In calculating uptake of particulate phase chemicals, it is necessary to specify regional deposition fractions (Equations 5 through 7). A primary environmental determinant of these fractions is particle diameter. The mean diameter for MS has been reported to range from 0.1μ to 1μ (Carter and Hasegawa, 1975; Hiller et al., 1982), and from 0.01μ to 0.8μ for SS. For the calculations reported here, a Mass Median Aerodynamic Diameter or MMAD of 0.7μ is used for MS (Stöber, 1984) and a MMAD of 0.4μ is assumed for fresh diluted SS (Wells, 1988). The particle diameters are assumed to be distributed lognormally with a geometric standard deviation (GSD) of 1.5 (Stöber, 1984).

Aged air, however, may contain a different distribution of aerosol sizes. Several authors (Keith and Dennick, 1960; Wynder and Hoffman, 1967; Ingebrethsen and Sears, 1985) have demonstrated that the MMAD for cigarette smoke decreases by a factor of 2 to 3 due to aging. This appears to be due to the loss of large particles from the suspended aerosol, as may be seen in the measured and predicted distributions published by Nazaroff and Cass (1989). An additional factor may be the "boiling off" of chemicals from the RSP. The present report, therefore, assumes that the MMAD for aged ETS is on the order of 0.15μ, and that for direct smoking is 0.7μ.

Total deposition of smoke in the lung has been reviewed by Stöber (1984), based primarily on studies by Hiller et al. (1982), Mitchell (1962), and Polydorova (1961). These results suggest that as much as 80% of the MS particulates are deposited in the lung (i.e., $f_{NP} + f_{TB} + f_P = 0.8$), while 10% to 20% of the ETS particulates are deposited. The value for ETS is consistent with the predictions of total lung deposition from an age-dependent model by Crawford (1982, 1983), which yields values of 1%, 4%, and 10% for f_{NP}, f_{TB}, and f_P, respectively, for a MMAD of 0.15μ.

The very high value of total deposition in active smokers appears to arise from several factors. The first is hygroscopic growth, which may be expected to double the size of particulate MS from 0.7μ to 1.4μ (Ishizu et al., 1980). The second factor is breath-holding, in which cigarette smoke is held in the lungs for several seconds prior to exhalation. If the model of Crawford (1982, 1983) is used with a breath-holding period of 3 seconds, particle diameters of 1.4μ are predicted to yield values of 1%, 15%, and 60% for f_{NP}, f_{TB}, and f_P, respectively. Since these sum to approximately the 80 percent reported in experiments, these values will be assumed here. Hygroscopic growth of ETS particles will not be assumed, since the inhaled and exhaled particles appear to be of the same diameter (Hiller et al., 1982).

As described previously, the total intake of RSP is assumed to be 240 mg in an active smoker and 3 mg in a passive smoker in our example. Using these values in conjunction with the estimates of f_{NP}, f_{TB}, and f_P from Equations 5 through 7, the calculated daily uptakes in mg by lung region are 12 mg, 36 mg and 144 mg for the NP, TB and P regions of the active smoker; 0.03 mg, 0.12 mg and 0.3 mg for the NP, TB and P regions of the passive smoker.

C.5. INTEGRAL ORGAN BURDENS FOR THE LUNG

C.5.1. Integral Organ Burden from RSP

Due to the very low assumed deposition fractions in the NP region, the focus of this discussion will be on the TB and P regions.

Translocation of the particles is on the mucus layer, which is driven forward towards the esophagus by the cilia. The velocity of this mucus blanket decreases dramatically in the deeper sections of the TB region. As a result, the length of time a particle resides in the lung depends critically on the site of deposition. Data on the removal of radiolabeled particles, however, show that removal from the TB region generally may be characterized by two phases. The first is a rapidly cleared phase, dominated by particles deposited on the mucus of the upper passageways. The second is dominated by particles deposited on the slowly moving mucus of distal passageways. Both phases are controlled primarily by the movement of the mucus and the site of deposition of the particles rather than on the chemical nature of the particles. It is possible, therefore, to use the results of the radiolabeled aerosol studies to estimate the retention of particulate ETS in the TB region.

Crawford and Eckerman (1983) have used the deposition model of Crawford (1982) and a model of mucus movement, in conjunction with measurements of retention of radiolabeled aerosol particles in healthy (non-smoking) human lungs, to develop predictive equations of retention. These retention functions contain two exponentials, corresponding to the two removal phases described above. The parameters in these equations depend upon the aerosol diameter and breathing characteristics. The general form of the equation is:

$$R(t) = (1 - b)e^{-0.693t/C_1} + b\,e^{-0.693t/C_2}$$

where t is the time since uptake into the TB region (in minutes). The parameter b is a function of median aerosol diameter, age, the GSD of the particle distribution and breathing characteristics. This parameter value equals the fraction of deposited particles found in the slowly removed component. The parameters C_1 and C_2 are the removal half-times for the rapid and slow components, respectively.

As described earlier, the MMAD for ETS particles is 0.15μ, with a GSD of 1.5. Applying the results of Crawford and Eckerman (1983) to ETS, yields values for b, C_1, and C_2 of 0.98, 450, and 710 minutes, respectively. For a MMAD of 1.4μ and a GSD of 1.5, the values of b, C_1, and C_2 are 0.82, 280, and 700 minutes, respectively. The flow of mucus in the TB region of active smokers, however, is reduced by a factor of 2 (Albert et al., 1975; Wanner et al., 1973). If the parameter values for 1.4μ in normal (non-smoking) lungs are changed to reflect the condition of slowed mucus, the half-times in the retention function would be doubled. For active smokers, therefore, C_1 and C_2 would be 560 minutes and 1400 minutes, respectively. The value of b should be unchanged.

The daily integral organ burden to the TB region from RSP may be obtained from Equation 15 by setting K equal to unity, f equal to f_{TB}, C × V equal to the daily intake of RSP, and T equal to 1440 minutes (24 hours). Using these values, the daily RSP integral organ burden to the TB region is 64,873 and 122 mg-minutes for the active and passive smokers in our example, respectively.

Solubilization and engulfment by macrophages generally dominate removal from the P region of the lung. Unfortunately, few data are available on the removal of RSP from the deep lung. It is known, however that the constituent chemical nicotine deposited in active smokers is highly soluble in lung fluid (Janoff et al., 1987). Black and Pritchard (1984) have found an alveolar retention half-time of 17 hours for RSP in active smokers, which will be used in our example. Similar measurements in passive smokers are not available. At this time, we use the same half-time for both passive and active smokers. Additional research is needed to accurately quantify removal of RSP in passive smokers. As a first approximation, a half-time of 17 hours for RSP removal will be assumed for both active and passive smokers (Wells, 1988). The retention function for the P region is

$$R(t) = e^{-0.693t/1020},$$

where t is in minutes since deposition. From Equation 15 for f_p and the daily intakes of RSP described earlier, the daily integral organ burden to the P region is 1.9×10^5 mg-minutes in active smokers and 390 mg-minutes in passive smokers.

C.5.2 Lung Integral Organ Burden from Particulate Chemicals

Chemicals should solubilize from the RSP at different rates, thereby affecting dose rate to the lung. Data to differentiate between chemical dose rates, however, are not available. The retention half-times used earlier will, therefore, be used here for other chemicals contained in particles. The ratio of integral organ burdens from chemical components, relative to RSP values, may be obtained from the ratio of intakes of those chemicals in the particulate phase shown in Table C-3. Daily integral organ burden to the lung by chemicals in the particulate phase have been calculated for the active and passive smoker of our example and are displayed in Table C-5.

C.6. CALCULATIONS FOR NICOTINE AND COTININE

The intake of nicotine by the active and passive smoker in the example described come from the particulate and vapor phases, respectively (Eudy, 1986). Leaderer (1988) gives the percentage of nicotine in the vapor phase of ETS as 95+, while Pritchard (1990) gives it as 70%.

TABLE C-5. DAILY INTEGRAL ORGAN BURDENS* FOR PARTICULATE PHASE CHEMICALS AS CALCULATED IN THIS REPORT
All Doses Are in mg-Minutes

Constituent	IB_P^{TB}	IB_P^P	IB_A^{TB}	IB_A^P
RSP	122	390	6.5×10^{4}	1.9×10^{5}
Nicotine	0	0	3.9×10^{3}	1.1×10^{4}
2-Naphthylamine	2×10^{-4}	6.2×10^{-3}	5.4×10^{-3}	0.016
4-Aminobiphenyl	5.6×10^{-4}	1.7×10^{-3}	1.4×10^{-2}	0.04
Benz(a)anthracene	5.2×10^{-4}	1.5×10^{-3}	0.14	0.4
Benzo(a)pyrene	3.2×10^{-4}	9.3×10^{-4}	0.08	0.24
λ-Butyrolactone	2×10^{-4}	5.8×10^{-4}	0.04	0.12
N-nitrosonornicotine	1.1×10^{-2}	3.1×10^{-2}	0.004	0.012
N-nitrosodiethanolamine	2×10^{-4}	5.8×10^{-4}	0.14	0.4
Nickel	3.8×10^{-3}	1.1×10^{-2}	0.14	0.4

* Superscript on IB indicates lung region (TB for tracheobronchial and P for pulmonary), and the subscript indicates passive (P) or active (A) smoker.

Our calculations, which presume that nicotine is entirely in the particulate phase for active smokers and entirely in the vapor phase for passive smokers, have been given in Table C-3. Nicotine concentrations have been measured in body fluids of active and passive smokers following known experimental exposure, providing information that can be applied to dosimetry calculations. Jarvis et al. (1984) have reported the results of nicotine measurements, which are summarized in Table 8-3 of the NRC report (1986). The nicotine/cotinine in the body fluids of passive smokers tends to be about 1% of the levels in active smokers.

As measured by Jarvis et al. (1988), Sepkovic et al. (1986), Kyerematen et al. (1982), and Benowitz et al. (1983), the clearance half-time for cotinine from the systemic body organs is on the order of 15 hours in active smokers. Sepkovic et al. (1986) suggest that this value for passive smokers is close to 45 hours. Their published data, however, indicate a half-time closer to 25 hours, a conclusion agreed upon by Jarvis et al. (1988). The half-time of 25 hours is more consistent with the measurements of urine excretion (Jarvis et al., 1988), where the half-time in passive smokers was 33 hours and in active smokers was 22 hours. This suggests that the passive-to-active ratio of half-times for removal of cotinine is about 1.5. For this ratio of excretion half-times, the data on body fluids (Jarvis et al., 1984) suggest that passive smokers take nicotine into their blood at a rate of 0.01/1.5 times the rate in active smokers, i.e., about 0.7% of the rate in active smokers. If it is assumed further that nicotine requires the same length of time to traverse the alveolar cells in passive and active smokers, a topic on which no data are available, then the ratio (active:passive) of integral organ burden for blood will equal approximately the ratio of rates into the bloodstream. This conclusion requires the assumption that the GI tract does not contribute significantly to the nicotine in the bloodstream. Data on nicotine absorption are not available at present. Since the nicotine dose to the P region is 11,000 mg-minutes for active smokers (see Table C-5), the integral organ burden to the lungs of passive smokers from vapor phase nicotine to this region will be approximately 80 mg-minutes

(or 11,400 × 0.007). For the TB region, the integral organ burden to the lungs will be 3900 × 0.007 or 27 mg-minutes. Neither the TB nor P region integral organ burdens are affected if the fraction of nicotine in the vapor phase is set equal to 70% instead of 100%. This invariance is due to the reliance on measured blood uptake for the calculation of integral organ burdens.

There is little available information on the uptake of chemicals to the bloodstream from which to calculate systemic organ doses. Again, nicotine/cotinine is an exception since measurements of body fluid concentrations and clearance half-times are available. As described above, nicotine is highly soluble in lung tissue, which implies that $f_{P,b}$ and $f_{TB,b}$ in Equation 19 are approximately 1. Thus, the uptake of nicotine to the bloodstream then equals the uptake into the P and TB regions of the lung. Once in the bloodstream, nicotine is converted to cotinine, as described by Jacob et al. (1988). This metabolic model is shown in Figure C-3, from which it may be seen that 70% of the nicotine is converted to cotinine, 9% goes directly to the urine, and 4% is metabolized to nicotine n-oxide. The remaining 17% is unaccounted for at present.

Nicotine is removed from the blood with a half-time of 2 hours in smokers (Jacob et al., 1988; Benowitz et al., 1982). As described above, the ratio of removal half-times for cotinine in passive and active smokers is 1.5. If this same ratio applies to the conversion of nicotine, passive smokers would display a removal half-time of 3 hours. If this ratio does not apply, both groups would possess a half-time of 2 hours. The retention function for nicotine then is either

$$R(t) = e^{-0.693t/2}$$

or

$$R(t) = e^{-0.693t/3},$$

depending on whether the removal half-time is 2 or 3 hours, respectively; t is in hours. Applying Equation 23, the daily integral organ burden from nicotine to the systemic organs of active

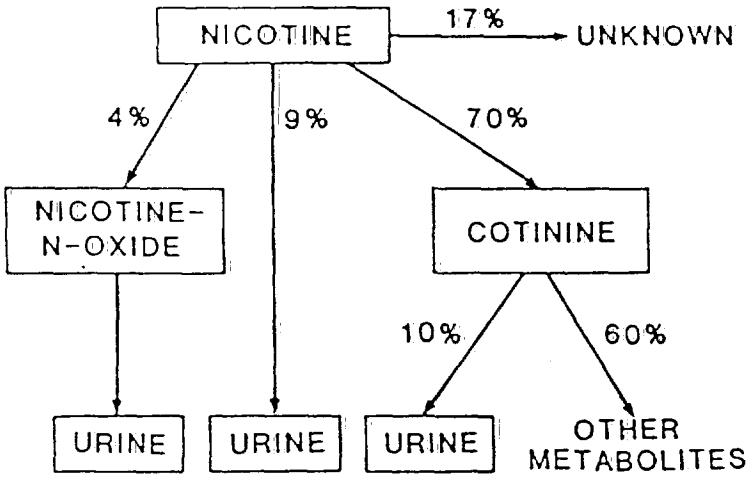

FIGURE C-3. A METABOLIC MODEL FOR THE CONVERSION OF NICOTINE AND THE EXCRETION

smokers is 2000 mg-minutes. The daily dose from nicotine to the systemic organs of passive smokers, using 0.7% of the value in active smokers, as discussed above, is approximately 16 mg-minutes if the half-time is 2 hours, and 27 mg-minutes if the half-time is 3 hours. Since the data of Kyerematen et all (1982) and Lee et all (1987) suggest that the rate of metabolism of nicotine is higher in active smokers, the latter value of 27 mg-minutes appears to be the best estimate.

The calculation of systemic organ doses from cotinine is more complicated than Equation 15, since cotinine is a metabolic product. The burden of nicotine in the blood at any time, t, after an uptake U_n is

$$B_n(t) = U_n e^{-0.693t/T},$$

where T is the removal half-time for nicotine (either 2 or 3 hours). The differential equation describing the rate of change of the burden of cotinine, $B_c(t)$, in blood then is:

$$\frac{dB_c(t)}{dt} = 0.693B_n(t)/T_c - 0.693B_c(t)/T_e, \qquad (26)$$

where T_c is the conversion half-time from nicotine to cotinine and T_e is the elimination half-time for cotinine from the body (15 hours in smokers and 25 hours in passive smokers). The burden of cotinine is obtained by solving Equation 26 to yield

$$B_c(t) = \frac{\lambda_c U_n(e^{-\lambda t} - e^{-\lambda_e t})}{(\lambda_e - \lambda)} \qquad (27)$$

where

$$\lambda_c = 0.693/T_c$$
$$\lambda_e = 0.693/T_e$$
$$\lambda = 0.693/T$$

and U_n is 10.6 mg in the active smoker and 0.08 mg in the passive smoker. The dose from cotinine then is obtained from Equations 12 and 13. The value of T_c is equal to T/0.7, where 0.7 is the fraction of nicotine converted to cotinine. The daily integral organ burden to the systemic organs of the active smoker then is 7660 mg-minutes. The daily integral organ burden to the passive smoker is approximately 145 mg-minutes if T is three hours and 140 mg-minutes if T is two hours. The measures calculated for nicotine and cotinine, and their ratios in MS to ETS, are included in Table C-6 and C-7.

TABLE C-6. SUMMARY OF DOSE MEASURES CALCULATED IN THIS REPORT (FOR OTHER PARTICULATE PHASE DOSES, SEE TABLE C-5)

Constituent	Measure	Value
1. Total RSP	Intake	P* = 3 mg A* = 240 mg
	Uptake	
	a. NP region	P = 0.03 mg A = 12 mg
	b. TB region	P = 0.12 mg A = 36 mg
	c. P region	P = 0.3 mg A = 144 mg
	Integral Organ Burden	
	a. NP region	P = na**
	b. TB region	P = 122 mg-min. A = 64,873 mg-min.
	c. P region	P = 390 mg-min. A = 1.9×10^5 mg-min.
2. Nicotine (particulate)	Intake	P = 0 mg A = 14 mg
	Uptake	
	a. NP region	P = 0 mg A = 0.72 mg
	b. TB region	P = 0 mg A = 2.2 mg
	c. P region	P = 0 mg A = 8.6 mg

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TABLE C-6. (continued)

Constituent	Measure	Value
	Integral Organ Burden	
	a. NP region	P = 0 mg A = na
	b. TB region	P = 0 mg A = 3800 mg-min.
	c. P region	P = 0 mg A = 11,000 mg-min.
	d. Systemic organs	P = 0 A = 2000 mg-min.
3. Cotinine (particulate)	Integral Organ Burden to systemic organs	P = 0 A = 7600 mg-min.
4. Nicotine (vapor)	Intake	P = 0.37 mg A = 0 mg
	Uptake	
	a. NP region	P = na A = 0 mg
	b. TB region	P = na A = 0 mg
	c. P region	P = 0.06 mg A = 0 mg
	Integral Organ Burden	
	a. NP region	P = na A = 0 mg
	b. TB region	P = 27 mg-min. A = 0 mg-min.
	c. P region	P = 80 mg-min. A = 0 mg-min.

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TABLE C-6. (continued)

Constituent	Measure	Value
	d. Systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 16 mg-min. A = 0 mg-min.
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 27 mg-min. A = 0 mg-min.
5. Cotinine (vapor)	Integral Organ Burden to systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 140 mg-min. A = 0 mg-min.
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 145 mg-min. A = 0 mg-min.
6. Nicotine (total)	Intake	P = 0.37 mg A = 14 mg
	Uptake	
	a. NP region	P = na A = 0.72 mg
	b. TB region	P = na A = 2.2 mg
	c. P region	P = 0.06 mg A = 8.6 mg
	Integral Organ Burden	
	a. NP region	P = na A = na
	b. TB region	P = 27 mg-min. A = 3800 mg-min.
	c. P region	P = 80 mg-min. A = 11,000 mg-min.

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TABLE C-6. (continued)

Constituent	Measure	Value
	d. Systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 10 mg-min A = 2000 mg-min
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 27 mg-min A = 2000 mg-min
7. Cotinine (total)	Integral Organ Burden to systemic organs	
	i. Passive smoking Conversion $T_{½}$=2 hrs.	P = 140 mg-min. A = 7660 mg-min
	ii. Passive smoking Conversion $T_{½}$=3 hrs.	P = 145 mg-min. A = 7660 mg-min
8. Benzene	Intake	
	i. Using fresh SS	P = 21 μg A = 300 μg
	ii. Using aged SS	P = 65 μg*** A = 300 μg
9. Hydrazine	Intake	
	i. Using fresh SS	P = 8 ng A = 300 ng
	ii. Using aged SS	P = 8 ng*** A = 300 ng
10. N-nitroso-dimethylamine	Intake	
	i. Using fresh SS	P = 160 ng A = 300 ng
	ii. Using aged SS	P = 80 ng*** A = 300 ng

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TABLE C-6. (continued)

Constituent	Measure	Value
11. N-nitroso-diethylamine	Intake	
	i. Using fresh SS	P = 48 ng A = 200 ng
	iii. Using aged SS	P = 48 ng*** A = 200 ng
12. N-nitroso-pyrrolidine	Intake	
	i. Using fresh SS	P = 32 ng A = 200 ng
	ii. Using aged SS	P = 32 ng*** A = 200 ng

* P ≡ Passive, A ≡ Active.

** na = not available for calculation due to insufficient information.

*** Obtained by multiplying the passive smoking intake for fresh SS by R, where R is the ratio of the concentration of the chemical relative to nicotine in aged SS to the concentration of the chemical relative to nicotine in fresh SS.

TABLE C-7. SUMMARY OF RATIO OF MEASURES (ETS/MS) CALCULATED IN THIS REPORT

Measure of Dose	Ratio
1. Intake of Total RSP	0.013
2. Uptake of Total RSP	
a. NP region	0.0025
b. TB region	0.003
c. P region	0.002
3. Integral Organ Burden of Total RSP	
a. NP region	na*
b. TB region	0.002
c. P region	0.002
4. Intake of Particulate Nicotine	0
5. Uptake of Particulate Nicotine	
a. NP region	0
b. TB region	0
c. P region	0
6. Integral Organ Burden of Particulate Nicotine	
a. NP region	0
b. TB region	0
c. P region	0
d. Systemic organs	0
7. Integral Organ Burden of Cotinine (from particulate nicotine)	
a. Systemic organs	0
8. Intake of Vapor Nicotine	Very large†
9. Uptake of Vapor Nicotine	Very large
10. Integral Organ Burden of Vapor Nicotine	
a. NP region	Very large
b. TB region	Very large
c. P region	Very large
d. Systemic organs	Very large

(continued on following page)

TABLE C-7. (continued)

Measure of Dose	Ratio
11. Integral Organ Burden of Cotinine (from vapor nicotine)	
a. Systemic organs	Very large
12. Total Intake of Nicotine	0.03
13. Total Integral Organ Burden of Nicotine	
a. NP region	na
b. TB region	0.01
c. P region	0.01
d. Systemic organs	
i. Passive smoking Conversion $T_{½}$ = 2 hours	0.01
ii. Passive smoking Conversion $T_{½}$ = 3 hours	0.015
14. Total Integral Organ Burden of Cotinine (Systemic organs)	
i. Passive smoking Conversion $T_{½}$ = 2 hours	0.02
ii. Passive smoking Conversion $T_{½}$ = 3 hours	0.02
15. Intake of Benzene	
a. Using fresh SS	0.07
b. Using aged SS	0.2
16. Intake of Hydrazine	
a. Using fresh SS	0.03
b. Using aged SS	0.03
17. Intake of N-nitrosodimethylamine	
a. Using fresh SS	0.5
b. Using aged SS	0.3
18. Intake of N-nitrosodiethylamine	
a. Using fresh SS	0.2
b. Using aged SS	0.2
19. Intake of N-nitrosopyrrolidine	
a. Using fresh SS	0.15
b. Using aged SS	0.15

*na ≡ not applicable due to lack of data.
†Very large occurs when the value for active smokers is zero.

APPENDIX D

ALTERNATIVE APPROACHES FOR ESTIMATING THE YEARLY NUMBER OF LUNG CANCER DEATHS IN NON-SMOKERS DUE TO ETS BASED ON DOSE-RESPONSE MODELING

D.1. INTRODUCTION

In Chapter 4 the annual number of lung cancer deaths attributable to ETS was estimated from epidemiological case-control and cohort studies. This appendix investigates alternative methods based on dose-response modeling techniques.

In order to use dose-response modeling approaches to directly estimate the number of lung cancer deaths in nonsmokers attributable to ETS, three elements are required:

1. the distribution of the time-weighted exposure of ETS in the nonsmoking population,
2. the age distribution of the nonsmoking population, and
3. a mathematical dose-response model describing the relationship between the age-specific lung cancer rate and the independent variables age, sex, race, and ETS exposure.

The U.S. EPA has already collected sufficient information so that elements 1 and 2 can be approximated with reasonable accuracy in a straightforward manner. A discussion of potential methods for the derivation of the dose-response model, element (3), is the subject of this appendix.

Three independent approaches are identified for estimating the dose-response relationship between age-specific lung cancer death rates and ETS. Each of these methods has its advantages and disadvantages in estimating ETS cancer risk. Presently, none of them is developed in full detail. The purpose of presenting these preliminary approaches is to invite comment on their relative merit, solicit advice on other potential approaches that might be investigated, and to help prioritize further research efforts in this area. Much of the material

considered here is based on ongoing research that is not fully documented at this time, and it is presented as an illustration of the type of approach that could be taken.

The three proposed general approaches for deriving ETS dose-response models are:

1. Establish a dose-equivalent relationship between ETS and a positive control such as inhaled benzo[a]pyrene (B[a]P) which has an animal-based inhalation cancer dose-response model associated with it. Heavy use would be made of animal carcinogen test results in this approach. This approach will be subsequently referred to as the **Relative Potency Approach** (RPA).

2. Establish an equivalency relationship between the number of cigarettes smoked per day and ETS exposure levels in mg/m^3 inhaled air. This relationship would then be used to estimate risk based on a direct state-of-the-art cigarette smoking dose-response model obtained from multiple sources of epidemiological data. This will be referred to as the **Cigarette-equivalent Approach** (CEA).

3. Use ETS epidemiological studies where a dose-dependent increase in the risk of nonsmoking women is associated with ETS. This will be referred to as the **Direct Approach** (DA).

Details concerning these approaches, examples of information that may be used in their conduct, and an evaluation of their strengths and weaknesses are presented in the following sections.

D.2. RELATIVE POTENCY APPROACH

D.2.1. Overview

The products of incomplete combustion from hydrocarbons (e.g., tobacco products) contain very complex mixtures of agents including thousands of polycyclic aromatic hydrocarbons (PAHs), many of which are known or suspected to be carcinogenic. The direct evidence for the carcinogenicity of hydrocarbon combustion products comes mainly from three types of information:

1. animal carcinogenicity tests of pure PAHs such as benzo[a]pyrene (B[a]P), etc., that are known to be formed as part of the combustion products of hydrocarbons,

2. animal carcinogenicity tests of condensates and various fractions of the condensates from hydrocarbon combustion products (e.g., coal flue gas, gasoline engine exhaust, diesel engine exhaust, coke oven emissions, etc.), and

3. human epidemiological studies (e.g., cigarette smoking, roofing tar fumes, coke oven emissions, etc.).

The EPA has historically used this type of information to help establish air quality criteria for emissions of complex mixtures of PAHs. In one situation a criterion for coke oven emissions was set based directly on epidemiological evidence of a dose-dependent increase in lung cancer (U.S. EPA, 1984). This evidence was gained from a long-term follow-up of black male workers who were working in close proximity to the coking operations in steel mills (Redmond et al., 1972). However, in most situations, direct evidence of the combined carcinogenic potency of the complex products of an emission source is not available. What often is available is information concerning the relative potency of complex PAH mixtures compared to a standard (such as B[a]P) obtained in experimental animal test systems (e.g., skin painting, lung implant, etc.). Data of this nature are not directly extrapolatable to humans due to our inability to establish equivalent exposure units for the experimental animal and anticipated human exposure routes. As a result, Albert et al. (1982) devised indirect methods for using relative potency information to estimate the risk due to inhalation of complex PAH mixtures. The general approach is to establish the relative potency of the complex PAH mixture compared to a standard agent that has a known inhalation dose-response model associated with it. Given the relative potency value, the exposure to the PAH mixture is converted into standard agent equivalent exposure units by taking the product of the PAH mixture exposure level and the relative potency. These standard equivalent exposure units are then substituted into the standard inhalation dose-response model to obtain cancer risk estimates that could be attributed to the complex PAH mixture. This general approach has been the guiding principal behind much of the PAH risk assessment research conducted by the EPA in recent years.

One view of ETS is that it is simply another complex mixture of agents containing multiple carcinogenic PAHs. Although ETS contains many carcinogens other than PAHs, recent research

(Grimmer et al., 1988) strongly suggests that the majority of ETS lung carcinogenic potency is due to the greater than 3-ring PAHs. This suggests that the same approaches for estimating lung cancer risk for complex PAH mixtures could also be employed to good advantage for estimating ETS lung cancer risk. Some of the information that could be useful in obtaining a cancer dose-response model for ETS using the general approach for PAHs is displayed in Table D-1.

D.2.2. Estimating ETS Relative Potency

The first step in obtaining an ETS dose-response model is to establish the relative carcinogenic potency of ETS compared to an appropriate standard (e.g., B[a]P, coke oven emissions, diesel engine exhaust). All of the available experimental information should be reviewed and evaluated for its quality and relevance in obtaining ETS relative potency estimates. One experiment that is a likely candidate for use in obtaining ETS versus B[a]P relative potency estimates is the lifetime rat lung implant study conducted by Grimmer et al. (1988). Due to its potential importance the protocol of that experiment is explained briefly. Three-month-old inbred Osborne-Mendel female rats were used. Various amounts of B[a]P or ETS fractions were dissolved in residue-free acetone, warmed to 50 degrees C, and a 1:1 mixture of beeswax and Trioctanoin was added. The acetone was removed by rotary evaporation under reduced pressure. This material was then warmed to 60 degrees C and introduced by injection into the left lobe of the lung of Nembutol-anesthetized animals following thoracotomy. Following its injection, the implant hardened into a pellet from which the test material diffused into the surrounding lung tissue. Following the test material injection, the thoracotomy aperture was sutured and the skin incision clipped. No further post-operative treatment was needed; operative and post-operative mortality was less than 5%. After surgery, rats were observed until

TABLE D-1. SELECTED SOURCES OF INFORMATION POTENTIALLY USEFUL FOR DERIVING A DOSE-RESPONSE RELATIONSHIP FOR ETS

Agent	Route of exposure in animal experiments			Human risk models based on epidemiological data where exposure is inhalation
	Skin painting	Lung implants	Inhalation	
Benzo[a]Pyrene (B[a]P)	X	X	X	
3-Methylcholanthrene (MCA)	X	X		
Artificial Complex PAH Mixture			X	
Coal Flue Gas Condensate	X	X		
Gas Engine Condensate	X	X		
Diesel Engine Exhaust	X	X	X	Under development
Sidestream Cigarette Smoke (ETS)		X	X no tumors induced	Possible to develop
Mainstream Cigarette Smoke	X	X	X	State-of-the-art model required
Coke Oven Emissions	X			Model available U.S. EPA (1984)
Aluminum Smelter Emissions	X			Upper bound under development
Roofing Tar Fumes	X			Out of date
Indoor Coal	X			Under development
Wood Combustion	X			Under development

their natural deaths which was as long as 32 months post exposure. Moribund animals were killed and when all animals were dead, complete autopsies were performed. The carcinogenic data obtained in the experiment are displayed in Table D-2. The historical control data for Osborne-Mendel rats are given in Table D-3, which are useful for obtaining stable non-zero estimates of the population background cancer rates.

The advantages of the Grimmer et al. (1988) study are:

- the cancer response is at the anticipated target site for ETS (i.e., the lung),
- the animals were observed for their full lifespan,
- the exposure was a continuous, lifelong leaching of the test material out of the beeswax/Trioctanoin pellet,
- multiple dose levels of the B[a]P positive control were employed,
- the average survival time for the experimental groups are given, which allows appropriate age adjustments to be made,
- the experiment is one of a series of six on complex PAH mixtures conducted by the same investigators that allows various hypotheses to be evaluated (e.g., dose additivity, irritation effects, etc.), and
- the experiments, quality control, and the investigators' reputations are of the highest order.

The disadvantages of the experiment are:

- exposure levels were most likely exponentially decreasing over time,
- the entire ETS condensate was not evaluated as one total exposure, and as a result, dose additivity of the ETS fractions must be assumed to obtain a relative potency estimate for the entire sample,
- the ETS condensate was not as aged as much as the ETS to which humans are expected to be exposed,
- multiple exposures were not given for the ETS fractions,

TABLE D-2. DATA THAT CAN BE USED TO OBTAIN RELATIVE POTENCY ESTIMATES FOR ETS CONSTITUENTS

Material	Dose mg x	Median survival t	Animals with epidermoid carcinomas/ Total animals
PAH-free material and PAH 2,3 rings	16.00	102	1/35
PAH 4 and more rings	1.06	105	5/35
Semivolatives (gaseous phase)	11.80	104	0/35
Benzo[a]Pyrene	0.03	93	3/35
	0.10	98	11/35
	0.30	75	27/35
Controls	Historical*	104	1/1945
	Vehicle	102	0/35
	Untreated	105	0/35

Source: Grimmer et al. (1988) and *Goodman et al. (1980)

TABLE D-3. HISTORICAL LUNG TUMOR CONTROL DATA FOR OSBORNE-MENDEL RATS

Lung tumors	Male	Female	Combined
Epidermoid Carcinomas	1/975	0/970	1/1945*
Alveolar/Bronchiolar Adenoma	4/975	2/970	6/1945
Alveolar Bronchiolar Carcinoma	3/975	3/970	6/1945

Source: Goodman et al. 1980
*Value used in ETS fraction relative potency estimation.

- the ETS mixture contains only the SS component and not the exhaled MS components of ETS, and
- the tumors were epidermoid carcinomas at the implant site rather than the alveolar-bronchiolar carcinomas usually associated with cigarette smoke.

The relative potency estimates of the ETS fractions and the theoretical estimates of the total emission based on the assumption of dose additivity are displayed in Table D-4. The dose additivity assumption has been shown to be consistent with information obtained in the same animal model system employing diesel or gas engine exhaust condensate. It is estimated that more than 70% of the total carcinogenic potency of the ETS is due to the 4 or more ringed PAHs (i.e. [.03673 x .05833]/.00302 = .7098). The relative potency estimates incorporate a special case of a two-stage mathematical model where the first stage preneoplastic clone has no selective advantage over normal tissue in the rat lung. The U.S. EPA is developing this model to estimate the relative potencies of other complex PAH mixtures whose carcinogenicity has been evaluated by the lung implant experimental system (Thorslund 1990).

TABLE D-4. RELATIVE POTENCY ESTIMATES OF ETS CONSTITUENTS*

Constituents	j	Dose mg. (x_j)	Fraction sample (f_j)	Maximum likelihood relative potency estimates (ρ_j)	% of total carcinogenicity attributable to constituent
PAH-free PAH 2,3 rings	1	16.00	0.55440	0.00158	29.02
PAH 4 and more rings	2	1.06	0.03673	0.05833	70.98
Semivolatiles (gaseous phase)	3	11.80	0.40887	0.00000	0.00
Weighted Total		28.86	1.00000	0.00302 = ρ_1	100.00

*Source of data: Grimmer et al. (1988)

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Refinements in the estimate and a more complete documentation of the techniques employed in the analysis are required. Also, results from other experimental systems should be used to estimate relative potencies if possible. The discussion given here should be regarded only as an illustration of the type of analysis that can be conducted with some of the available information.

D.2.3. Inhalation Dose-Response Models for PAHs

Once the relative potency of ETS to the standard agent (e.g., B[a]P) has been estimated, the result is used to estimate the standard equivalent exposure units which are substituted into the standard inhalation dose-response model to obtain cancer risk estimates. As indicated in Table D-1, a number of alternatives exist upon which a standard inhalation dose-response model could be based. We shall evaluate three potential choices in this section.

D.2.3.1. Hamster Inhalation B[a]P Dose-Response--The only animal pure PAH inhalation experiment presently available that contains sufficient information to establish a dose-response relationship was conducted by Thyssen et al. (1981). In that study Syrian golden hamsters were exposed over their entire lifespan to pure B[a]P via an NaCl aerosol. The tumors most closely associated with B[a]P exposure were malignant and found in the larynx and pharynx. Summarized results of the study are displayed in Table D-5. Thorslund (1990) demonstrated that a two-stage model with exponential growth of preneoplastic targets can adequately describe the experiment. The advantages of using the Thyssen et al. (1981) study are:

- the exposure was well monitored over the entire length of the experiment,
- the average lifetime exposure and age at death was available for each animal in the experiment,

TABLE D-5. EXAMPLE OF ANIMAL INHALATION DOSE-RESPONSE MODEL SYRIAN GOLDEN HAMSTERS EXPOSED TO B[a]P VIA NaCl AEROSOL
(Thyssen et al. 1981)

Lifetime average exposure (mg/m^3 B[a]P) x	Average survival (weeks) t	Animals examined	# of hamsters with one or more malignant laryngeal or pharyngeal tumors	
			Observed	Predicted (sum of individual data)
Historical Controls	80.0	226	1	0.642
Matched Controls	105.0	22	0	0.179
Total Controls	-----	248	1	0.821
Low Exposure Chamber (2 mg/m^3) 0.250 mg/m^3	100.5	24	0	1.23
Middle Exposure Chamber (10 mg/m^3) 1.016 mg/m^3	102.5	23	11	8.55
High Exposure Chamber (50 mg/m^3) 4.292 mg/m^3	70.7	23	17	17.98

Model*

$$P(x,t) = 1 - \exp - H(x,t)$$

$$H(x,t) = \frac{A}{G^2}(1 + Sx)^2\{[\exp(Gt) - 1 - Gt]\}$$

$$A = 3.865 \times 10^{-7},\ S = 6.843,\ G = 0.0263$$

*Thorslund (1990)

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- the animals were followed for their entire natural lifespan, and
- careful histopathological examinations were conducted on each animal.

The disadvantages of this study are:

- the hamsters are not humans,
- the tumors did not develop at the site anticipated in humans (i.e., lung),
- the hamsters are resistant to lung tumor formation, and
- the bioavailability of the B[a]P/NaCl aerosol may be different from the bioavailability of the PAH-matrix to which humans are exposed.

When confronted with inhalation exposures of complex PAH mixtures, the approach used by the EPA program offices has usually been to assume that the entire PAH mixture is as potent as B[a]P and to substitute the total exposure units into an earlier version of the B[a]P dose-response model derived from the Thyssen et al. (1981) data. This approach is recognized as having numerous uncertainties and as being conservative.

D.2.3.2. Rat Inhalation Diesel Engine Exhaust Dose-Response--The diesel engine exhaust rat inhalation study of Mauderly et al. (1987) offers another possibility for establishing an inhalation dose-response model. The advantages of this study are:

- the tumors appeared in the lung,
- the PAH-matrix is reasonably similar to the type one might expect with human exposures, and
- the lung burden exposure measurements are available.

The disadvantages of this study are:

- the rats are not humans,
- the lung tumors were for the most part not malignant, and
- the relative potency estimates compared to B[a]P for the exact diesel engine emissions used in the experiment are not available.

The authors of the diesel engine exhaust paper obtained a dose-response model from their experiment results. However, their derived model would not be consistent with the usual regulatory assumption of low dose linearity. The same type of model employed for B[a]P could also be used for diesel engine exhaust. As a result, it would be desirable to acquire the individual animal data and fit the two-stage model to it to maintain a consistent approach throughout.

To use this study an estimate of the relative potency of ETS compared to diesel engine exhaust is required. Several options for obtaining such estimates exist. Perhaps the most direct approach would be to pool the data obtained in the Grimmer et al. (1987, 1988) papers on ETS and diesel engine exhaust which both employed the lung implant experimental system.

D.2.3.3. Human Inhalation Coke Oven Dose-Response--As noted previously, a dose-response model for coke oven emissions has been used by the U.S. EPA (1984). This model is based on a simple linear absolute risk model where the age-specific lung cancer risk is proportional to a lag-time adjusted cumulative exposure. The advantages of using this model are:

- it is based on human occupational epidemiological data,
- the coke oven exposure in inhaled air is comparable to how humans are exposed to ETS, and
- human coke oven inhalation data have been used by EPA to support regulatory decisions.

The disadvantages are:

- the model should be updated with regard to presently available mortality and exposure information, which would require considerable effort and resources,
- the cigarette smoking rates of the cohort members are unknown and thus are not adjusted for and could be an important confounding variable, and

- two different bioassay systems are required to obtain coke oven equivalent exposure units for ETS (i.e., ETS compared to B[a]P lung implant and coke oven emissions compared to B[a]P skin painting).

Re-evaluating the coke oven data using the same two-stage model approach employed for the other PAH data sets and the updated mortality experience appear to be a more scientifically sound path to follow, but would require substantial resources.

D.3. CIGARETTE-EQUIVALENT APPROACH

D.3.1. Overview

The most obvious approach for obtaining an inhalation dose-response model for ETS is to use direct cigarette smoking. The cigarette-equivalent approach (CEA) may be viewed as a special case of the RPA with an added complication. An adjustment is required to equate the lung deposition of carcinogens achieved by forced deep puffing on cigarettes with that resulting from normal inhalation of ETS in the surrounding air. In chapter 4 several approaches were discussed for making such adjustments that were felt to be inadequate. In this section an alternative general approach based on specific biological markers is suggested.

The three necessary elements required to develop a credible ETS dose-response model are:

- a state-of-the-art human mainstream smoke (MS) dose-response model,
- a relative potency estimate of ETS compared to MS, and
- a deposition rate equivalency for an appropriate biological marker (e.g., B[a]P-DNA adduct) between ETS and MS.

Each of these elements are discussed in the following sections.

D.3.2. State-of-the-Art Mainstream Cigarette Dose-Response Model

The ideal study for establishing a dose-response model for mainstream smoking would be based on a large cohort where many of the members had died of lung cancer, and the following information on each member of the cohort would be obtainable.

1. detailed smoking history
    a. age at start of smoking
    b. way of smoking
        i. inhalation patterns
        ii. average puffs per cigarette
        iii. length to which cigarette is smoked
    c. smoking intensity (i.e., number of cigarettes smoked per day)
    d. changing pattern of cigarette use over time
2. age at the start and end of the observation period and vital status at the end of the observation period.
3. most detailed pathology information available
4. demographic information
    a. race
    b. sex
    c. population density of domicile
    d. job status
5. workplace exposure to other known lung carcinogens

While the information contained in any actual conducted study will not even come close to conforming to the ideal, the list still is a convenient yard stick to measure potential studies for possible inclusion in our dose-response development. Different limited studies may be useful in contributing information concerning as little as one parameter in the eventual dose-response model.

D.3.2.1. Sources of Epidemiological Information Useful for Constructing a Dose-Response Model--A number of epidemiological studies may be viewed as primary sources of information concerning the dose-response relationship between mainstream cigarette smoke and lung cancer. These studies are briefly described below.

D.3.2.1.1. U.S. American war veterans (AWV). A cohort of about 300,000 American male war veterans was assembled in 1954 by Dorn and their mortality experience subsequently reported on by Kahn (1966), Rogot (1974), Whittemore (1988), and Freedman and Navidi (1989). This study includes information of age at start of smoking and number of cigarettes smoked per day. It also included ex-smokers. The study has the distinct advantage of having a total of 1266 lung cancer deaths available for analysis, and some details on individual cohort members are potentially obtainable from National Cancer Institute (NCI) data tapes. The study's disadvantages are that exposure information was only obtained at the beginning of the observation period so that changes in smoking patterns, except for stopping, cannot be taken into account. Also, there are no women in the cohort.

D.3.2.1.2. American Cancer Society (ACS) volunteers. The ACS enlisted the help of a large number of volunteer workers to help define and follow a cohort of about 440,000 male and 570,000 female predominantly middle to upper class white Americans. This study was reported by Hammond (1966) with additional information available from ACS personnel. The study is particularly useful in that it contains extensive information on women and nonsmokers not available from other sources. Additional advantages of the study are the large number of lung cancer deaths in the cohort, 1542 for male smokers and 164 for the females, and information on age when smoking started and length of follow-up is available for each cohort member. The

main disadvantages of the study are: (1) it took place over a relatively narrow time frame of 8.5 years which increases the potential for a calendar year bias, and (2) the lower social economic classes are under-represented which may introduce a bias due to the difference in type and way cigarettes are smoked.

D.3.2.1.3. British male physicians. Doll and Peto (1978) published the data shown in Table D-6 based on the information obtained by following the survival of a cohort of approximately 34,000 British male physicians. The smoking histories of each individual in the cohort were obtained by questionnaires at three different points in time. Table D-6 is a subset of the total cohort consisting of subjects who smoked at a nearly constant rate over their smoking lifetime. Due to the quality of the smoking information and pathology confirmation of most of the cases, this study is generally acknowledged to be the most informative available for establishing dose-response relationships. The disadvantages are that the number of observed lung cancer deaths are relatively small (i.e., 215), no women are included in the sample, and information on ex-smokers was never published in a form suitable for analysis. Also, a sample of physicians has a high potential for a sociological bias to be built into it. Ten years of additional observation is available on the cohort that has not yet been published and could be of considerable importance in the establishment of a dose-response model.

TABLE D-6. NUMBER OF LUNG CANCER DEATHS AND PERSON-YEARS OF OBSERVATION FOR BRITISH MALE PHYSICIANS

Mid-point age interval (years)		Average exposure (cigarettes per day)								
		0.0	2.7	6.6	11.3	16.0	20.4	25.4	30.2	38.0
42.5	observed lung cancer deaths	0.0	0.0	0.0	1.0	0.0	1.0	0.0	1.0	0.0
	person-years	17,846.5	1,216.0	2,041.5	3,795.5	4,824.0	7,046.0	2,523.0	1,715.5	892.5
47.5	observed lung cancer deaths	0.0	0.0	0.0	1.0	1.0	1.0	2.0	2.0	0.0
	person-years	15,832.5	1,000.5	1,745.0	3,205.0	3,995.0	6,460.5	2,565.5	2,123.0	1,150.0
52.5	observed lung cancer deaths	0.0	0.0	0.0	2.0	4.0	6.0	3.0	3.0	3.0
	person-years	12,226.0	853.5	1,562.5	2,727.0	3,278.5	5,583.0	2,620.0	2,226.5	1,281.0
57.5	observed lung cancer deaths	2.0	1.0	0.0	1.0	0.0	8.0	5.0	6.0	4.0
	person-years	8,905.5	625.0	1,355.0	2,288.0	2,466.5	4,357.5	2,108.5	1,923.0	1,063.0
62.5	observed lung cancer deaths	0.0	1.0	1.0	1.0	2.0	13.0	4.0	11.0	7.0
	person-years	6,248.0	509.5	1,068.0	1,714.0	1,829.5	2,863.5	1,508.5	1,362.0	826.0
67.5	observed lung cancer deaths	0.0	0.0	1.0	2.0	2.0	12.0	5.0	9.0	9.0
	person-years	4,351.0	392.5	843.5	1,214.0	1,237.0	1,930.0	974.5	763.5	515.0
72.5	observed lung cancer deaths	1.0	1.0	2.0	4.0	4.0	10.0	7.0	2.0	5.0
	person-years	2,723.5	242.0	696.5	862.0	683.5	1,055.0	527.0	317.5	233.0
77.5	observed lung cancer deaths	2.0	0.0	0.0	4.0	5.0	7.0	4.0	2.0	2.0
	person-years	1,772.0	208.5	517.5	547.0	370.5	512.0	209.5	130.0	88.5

Source: Doll and Peto (1978)

D.3.2.1.4. Other data sources. Other sources of information that could prove useful in obtaining information on a dose-response model are Best (1966), Canadian smokers; Bross et al. (1968), individuals who switched to filter cigarettes; Cederlof et all (1975), a national probability sample of Swedish subjects; Graham and Levin (1971), individuals who stopped smoking; Hirayama (1977), Japanese smokers; Stevens and Moolgavkar (1984), British males; Lubin et al. (1984), individuals who changed smoking habits; Wald et al. (1988), U.K. smoking statistics; the IARC monograph on the evaluation of the carcinogenic risk of tobacco smoking to humans IARC (1986), general information; and the U.S. Public Health Service, Smoking and Health Report series for various types of smoking related information.

D.3.2.2. Modeling Approach for Cigarette Smoking Data--Various investigators, such as Doll and Peto (1978), Thorslund and Charnley (1987), Brown and Chu (1987), Gaffney and Altshuler (1988), Darby and Pike (1988), Freedman and Navidi (1989), and Moolgavkar et al. (1989), were successful in fitting various forms of multi-stage type models to the British physicians data. Modeling attempts using the AWV and ACS data have been less successful. Freedman and Navidi (1989) could not obtain adequate fits using standard multi-stage models to the AWV and ACS data sets when information on ex-smokers was included. The reasons for this inability could be either deficiencies in the multi-stage model (hypothesis put forth by the authors) or some unknown bias in the data that distorts the true dose-response relationship. To clarify the situation other modeling approaches should be attempted.

Probably the most successful approach for mathematically modeling cigarette smoking data was put forth by Moolgavkar et al. (1989). This is the only attempt to date to incorporate a promotional component of cigarette smoke into a dose-response model. Using Moolgavkar's basic model and the additional simplifying robust assumptions that:

- the number of stem (target) cells are constant over time,
- the ratio S of unit exposure induced to background cell transition rates are equal for the two cellular transitions (i.e., normal stem to preneoplastic and preneoplastic to neoplastic), and
- the growth rate of preneoplastic cells is a function, G(x), of the number of cigarettes smoked per day,

the age-specific lung cancer rate of an individual at age t who has smoked x cigarettes per day since age t_0 can be expressed as:

$$h(x,t) = \frac{A}{G(x)}(1+Sx)^2\{\exp[G(x)(t-t_0)]-1\}+\frac{A}{G(0)}(1+Sx)\exp[G(x)(t-t_0)]\{\exp[G(0)t_0]-1\}$$

where A is the product of the background transition rates, $G(x)=G(0)[1+(R-1)M(x)]$ with $R=G(\infty)/G(0)$ being the maximum relative growth rate increase that can be induced by cigarettes and M(x) is a still to be specified function that defines the fraction of the maximum growth rate increase that is induced with x cigarettes per day. In the model employed by Moolgavkar, the simplifying assumption $G(x)=G(0)+\Delta x$ was made. While this assumed relationship may be appropriate at low doses, it very likely results in a distortion of the effect for heavy smokers.

It is proposed that the Moolgavkar (i.e., two-stage) model parameter estimates be obtained by simultaneously using multiple epidemiological-smoking-lung cancer data sets and the following modifications and extensions of the above basic model:

- Moolgavkar assumed that the time from the development of a neoplastic cell until death due to a lung cancer was a constant 3.5 years for each of the lung cancer deaths. As an alternative this length of time will be estimated by maximum likelihood methods assuming:
  1. it is a constant unknown value for all lung cancer deaths, and
  2. it is a random variable with an integer gamma probability distribution.
- Alternative specific forms for G(x) will be specified based on various assumptions of how binding of smoking product agents with preneoplastic cells induce promotion.

- An adjustment will be made for the difference between British and American cigarettes and British and American smoking habits.
- An investigation will be made of the hypothesis that G(0) may be different pre- and post-exposure to accommodate the observation of rapidly falling age-specific rates post cessation of smoking.

The largest information data base possible will be used in fitting the different variations of the model. An illustration of how one of the parameters in the model, G(0), could be estimated is given below.

Hammond (1966) pooled the ACS lung cancer mortality data for men and women nonsmokers and obtained age-specific death rates for five-year age intervals. This information is displayed in Table D-7. The justification given by Hammond (1966) for pooling the data was the inability to reject the hypothesis of equal rates for the sexes on the basis of a statistical test. Under the assumption of no cigarette smoking, x=0, so the previously described age-specific rates for the two-stage model has the reduced form:

$$h(0,t) = \frac{A}{G(0)}\{\exp[G(0)t]-1\}$$

Assuming that the number of lung cancer cases out of the number of person years of observation was an independent binomial random variable for each age class, maximum likelihood estimates were obtained for the unknown parameters A and G(0) in the above model. The adequate fit of the model is displayed in Table D-7 and Figure D-1.

It is reasonable to assume that the parameter G(0) is human population independent and, perhaps, even species independent taken on a lifetime equivalent time scale. However, the value A would most likely be dependent on the environmental conditions an individual is living under. Therefore, different values for U.S. and British populations should be estimated.

TABLE D-7. LUNG CANCER DEATH RATES PER 100,000 PERSON-YEARS AND OBSERVED AND PREDICTED NUMBER OF LUNG CANCER DEATHS AMONG MEN AND WOMEN WHO NEVER SMOKED REGULARLY

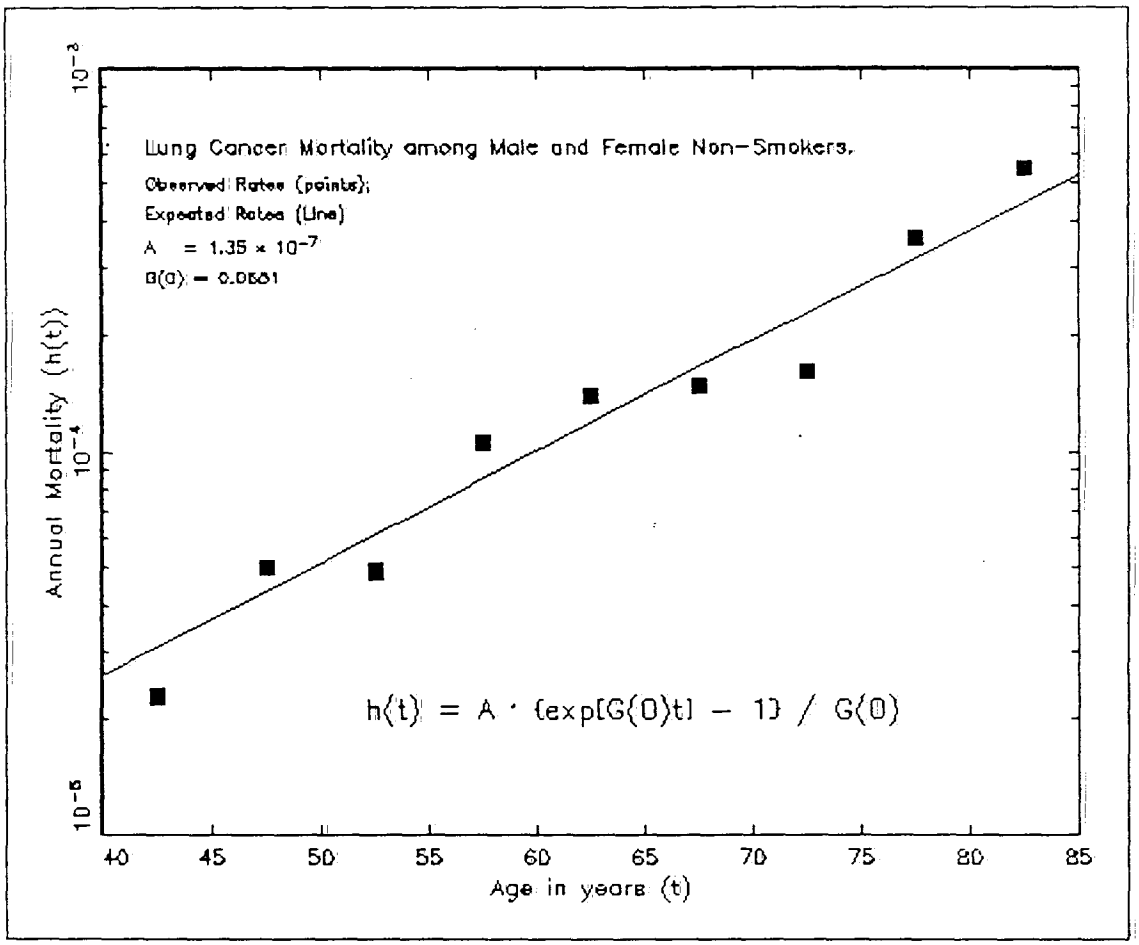
Age group L to L+5	Combined men and women			Population size N (person-years)
	Number of lung cancer deaths n		Death rate dr	
	Observed	Predicted		
40-44	4	5.40	2.3	173,913
45-49	16	14.01	5.0	320,000
50-54	16	20.05	4.9	326,531
55-59	30	24.52	10.5	285,714
60-64	32	27.53	13.9	230,216
65-69	26	29.43	14.7	176,871
70-74	18	25.84	16.1	111,801
75-79	21	18.82	35.8	58,659
80-84	14	11.41	54.6	25,641
Total	177	----		

Source: Hammond (1966)/ACS Study

* $N = \frac{nx10^5}{dr}$

calculated from data $\chi^2_7 = 7.036$ $p = 0.425$

FIGURE D-1.
GOODNESS-OF-FIT OF TWO-STAGE MODEL TO NON-SMOKERS' AGE-DEPENDENT LUNG CANCER DATA



Source of data: Hammond et al. (1966).

The obvious advantage of the proposed CEA is that it is based on the most extensive body of information concerning the dose-dependent effects of an environmental agent on a human cancer response that exists. The main disadvantages are the complexity of the analysis and the possibility of not establishing a credible ETS equivalency relationship. The latter factor is discussed in the next sections.

D.3.3. Estimation of the Relative Potency of ETS Compared to MS

Previous approaches for establishing ETS/cigarette equivalency (e.g., Darby and Pike, 1988) have made the implicit assumption that the ratio of the potency of emissions to some surrogate measure of internal exposure (e.g., nicotine, cotinine, etc.) is the same for ETS and MS. The large variability in relative potency estimates of complex-PAH mixtures that are displayed in Table D-8 suggests that the implicit assumption of equal potency is suspect.

Several methods can be used to estimate the ETS compared to MS relative potency. The inhalation studies in Syrian golden hamsters where laryngeal carcinomas were elicited from MS (Dontenwill et al., 1973; 1977) and from B[a]P (Thyssen, 1981) can be used to obtain a MS-to-B[a]P relative potency estimate. Dividing this obtained potency value into the ETS-to-B[a]P, the relative potency obtained from the lung implant studies discussed in Section D.1.3.1 would give a relatively potent estimate of ETS to MS. Stanton et al. (1972) conducted a lung implant study using cigarette smoke condensate (CSC). Unfortunately for our present purposes, 3-methylcholanthrene (MCA) was used as the positive control in the experiment so direct comparison with ETS is not possible. However, Grimmer and his colleagues for the most part closely adopted Stanton's experimental protocol for conducting lung implant studies. Thus, a direct pooling of the data in the Stanton and Grimmer experiments could logically be used to obtain a potency estimate. As an alternative, the two-step approach of estimating the potency of

TABLE D-8. RELATIVE POTENCY ESTIMATES OF COMPLEX MIXTURES OF INCOMPLETE COMBUSTION PRODUCTS OF HYDROCARBONS COMPARED TO B[a]P

Complex PAH exposure	Direct bioassay estimate* of relative potency
Coal Flue Gas Condensate	0.05444
Gas Engine Condensate	0.02190
Diesel Engine Exhaust	0.00230
Sidestream Cigarette Smoke	0.00302
Coke Oven Emissions	0.03180[a]

*Lung implant studies
[a]Skin painting

CSC compared to MCA from the Stanton experiment and then establishing the relative potency of MCA compared to B[a]P in another assay system (e.g., subcutaneous injection, skin painting, etc.) could be employed. A final alternative might be to compare the weighted relative potency estimates of the known constituents in the MS and ETS samples that have stable established estimates of their carcinogenic potency compared to B[a]P. One potential list of stable relative potency estimates developed by Thorslund (1990) is shown in Table D-9.

The last piece of information required to obtain an ETS risk model based upon the CEA is a deposition ratio estimate between MS via active smoking and ETS under normal inhalation conditions. One promising approach of using B[a]P-DNA-adducts and other endpoints as biomarkers is discussed in the next section.

D.3.4. Deposition Differences of Chemicals from Cigarette Smoke in Smokers and Nonsmokers

To obtain an equivalency relationship between MS and ETS, both potency and deliverable dose conversion factors are needed in order to use the MS-lung cancer data as a surrogate for lung cancer induced by ETS.

TABLE D-9. RELATIVE POTENCY ESTIMATES OF AGENTS COMPARED TO B[a]P

Agent	Relative potency	Source of estimate
Anthracene	0.00000	IARC adequately studied; no indication of carcinogenic effect category
Fluoranthene	0.00000	
Pyrene	0.00000	
Benzo[b]fluoranthene	0.12277	Deutsch-Wenzel et all (1983) (Grimmer's group) lung implant data Thorslund (1990) estimates
Benzo[k]fluoranthene	0.05322	
Benzo[j]fluoranthene	0.05232	
Benzo[e]pyrene	0.00704	
Benzo[a]pyrene	1.00000	
Indeno Pyrene	0.27800	
Benzo[ghi]perylene	0.02124	
Anthanthrene	0.31598	

Under the assumption that the PAHs possess most of the carcinogenic potency in MS and ETS, the deliverable target dose can be estimated by directly measuring the number of DNA adducts formed in people smoking different numbers of cigarettes per day and in people who are nonsmokers in the presence of smokers with different frequencies of smoking.

Specific adducts, such as the DNA 7,8-diol-9,10-epoxide of B[a]P which is present in both MS and ETS, can be detected using sensitive immunoassays or postlabelling DNA techniques (Shamsuddin et al., 1985; Randerath et al., 1986). Differences in adduct formation between smokers and nonsmokers varied depending on the experiment but was as high as 400-fold when DNA from oral mucosa was analyzed using the postlabelling technique. Hemoglobin adducts as markers of genotoxicity have been analyzed in smokers and nonsmokers where smokers had about a 7-fold greater number of adducts than nonsmokers.

Indirect measures of dose between smokers and nonsmokers may also be available in which gene mutations can be measured in peripheral leukocytes at the Hypoxanthine phosphoribosyl transferase locus as well as other loci. In fact, such a test could conceivably be used directly to obtain a cigarette equivalence estimate without making potency difference adjustments. Other genetic damage tests, such as chromosomal aberrations and sister chromatid exchanges, may also be useful in determining deliverable target dose information for smokers and nonsmokers exposed to ETS.

To obtain an equivalency relationship of deliverable dose between smokers and nonsmokers, a thorough review of the literature for articles that show dose-response relationships between MS/ETS and DNA adducts, protein adducts, and gene mutations should be conducted and the most appropriate endpoints selected for use in the equivalency estimate. The main advantage of the approach is the high suspected correlation of the endpoint with the cancer response. The main disadvantage is the discounting of potential agents that act exclusively as promoters.

D.4. DIRECT APPROACH

The most straightforward approach for estimating ETS lung cancer risk is to estimate ETS exposure in a suitable cohort and follow the resulting mortality pattern over time. As of yet, no directly measured ETS exposure data exist on a cohort. The ideal in this regard would be personal monitoring data obtained from nonsmokers for an agent such as cotinine which is closely and uniquely associated with cigarette smoke. In this application, the use of cotinine is appropriate as long as it is linearly related to total ETS air levels. In lieu of such information, investigators have attempted to obtain surrogate measures of ETS. One such measure is the number of cigarettes smoked per day by the spouses of nonsmoking individuals. The quality of such a surrogate measurement depends upon: (1) the extent that nonsmokers are exposed to

smokers other than their spouses, (2) the consistency within the cohort of the husbands' and wives' spatial and time closeness, and (3) the consistency within the cohort of the fraction of the total cigarettes that are smoked by the spouse in the home. Due to sociological factors regarding a woman's place in Japan, the homogeneity of the Japanese society, and the small, close living arrangements of Japanese couples, probably the best surrogate measure of ETS exposure available is the number of cigarettes smoked per day by the husbands of Japanese women. The person-years of observation and the number of lung cancer deaths for Japanese women classified in regard to their husband's age and smoking habits obtained in the prospective study conducted by Hirayama (1984) is displayed in Table D-10. Under the assumption that all the excess lung cancer risk in Japanese women was due to husband-produced ETS exposure in the home, crude risk models can be generated from the information supplied in Table D-10. Better estimates could be obtained if information such as the length of marriage, wife's age, age husband started smoking, and smoking habits of wife's parents were available for individual cohort members. A fair amount of such information has been generated by Hirayama (1984) but presently is not reported in the open literature. Gaining access to the data could prove valuable.

TABLE D-10. LUNG CANCER MORTALITY IN JAPANESE WOMEN BY HUSBAND'S AGE GROUP AND SMOKING HABITS (PATIENT HERSELF A NON-SMOKER)*

Husband's age group	Husband's smoking habit											
	Non-smoker		Ex-smoker		1-14/day		15-19/day		20+/day		Total	
40-49	4	6,229	1	1,255	8	8,621	6	5,158	16	10,764	35	32,027
50-59	10	7,791	3	1,922	20	9,668	8	4,052	24	9,820	65	33,253
60-69	18	7,120	11	2,687	28	7,243	9	2,513	23	4,651	89	24,214
70-79	5	755	2	348	2	612	1	105	1	226	11	2,046
Total	37	21,895	17	6,212	58	26,144	24	11,828	64	25,461	200	91,540

*Number of lung cancer deaths out of number of wives in the same cross classification cell.
Source: Hirayama (1984).

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